Pharmacogenetic Activities in SWOG Breast Cancer

Pharmacogenomics: Future Plans

- **S8897 Adjuvant CMF vs. CAF/ no Treatment**
  - **Ambrosone RO1: Other genes (TBCI approved, analyses ongoing)**
- **S0221 Adjuvant Dose Dense vs. Dose Denser AC-T**
  - **Ambrosone: These and other genes (TBCI approved, collection ongoing)**
    - **Toxicities (short run)**
    - **Outcomes (long run)**
- **S0226 Metastatic anastrozole +/- fulvestrant**
  - **Susan Nowell RO1**
  - **ESR 1 and 2 (ER)**
  - **CYP19 (Aromatase)**
  - **CYP3A4, FMO3, UGT2B3, UGT2B10, SULT1E1 and SULT1A1**
- **ALL: Whole genome sequencing (PGRN collaborations) (Christine Ambrosone is applying for RO1 for S0221)**

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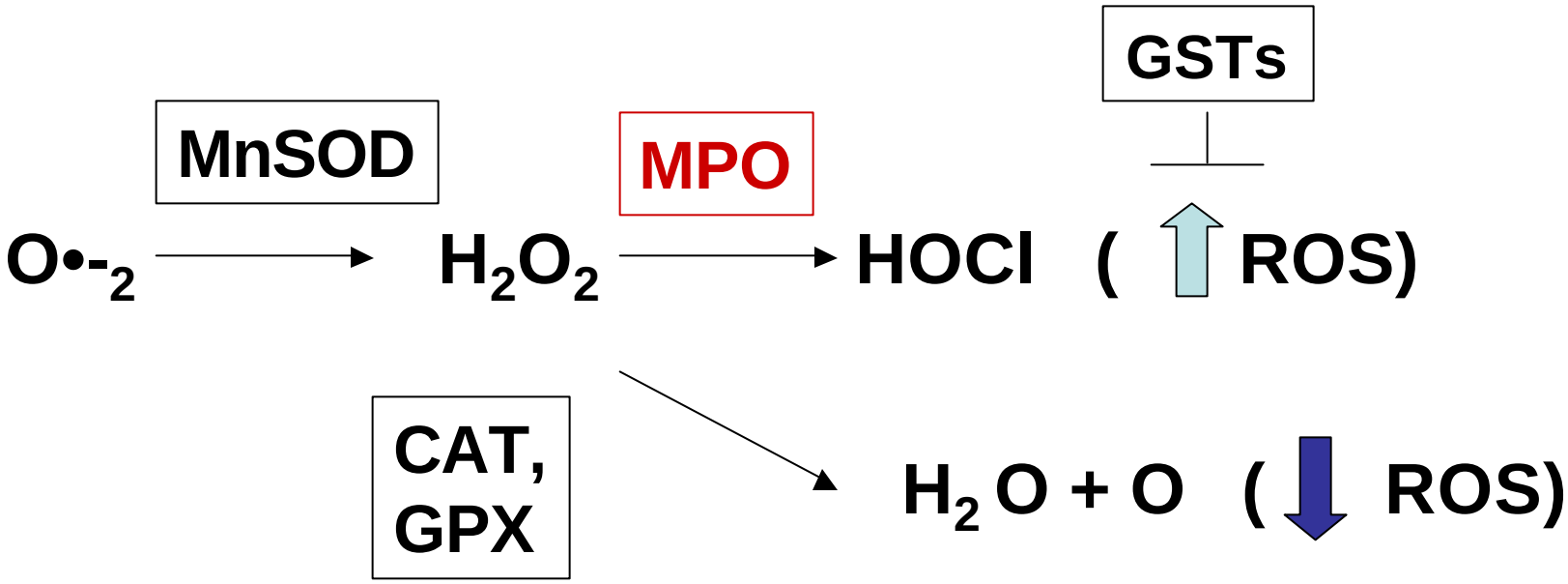
Inherited genetic variability Chemotherapy, Radiation and ROS

- **ROS/Oxidative stress induced by CTX:**
  - **–Damage to DNA**
  - **–Lipid peroxidation**
  - **–Protein modification**
  - **–Membrane disruption**
  - **–Mitochondrial damage**
  - **–Apoptotic cascade**
- **Inherited variability in generation of ROS could result in differential treatment outcomes**

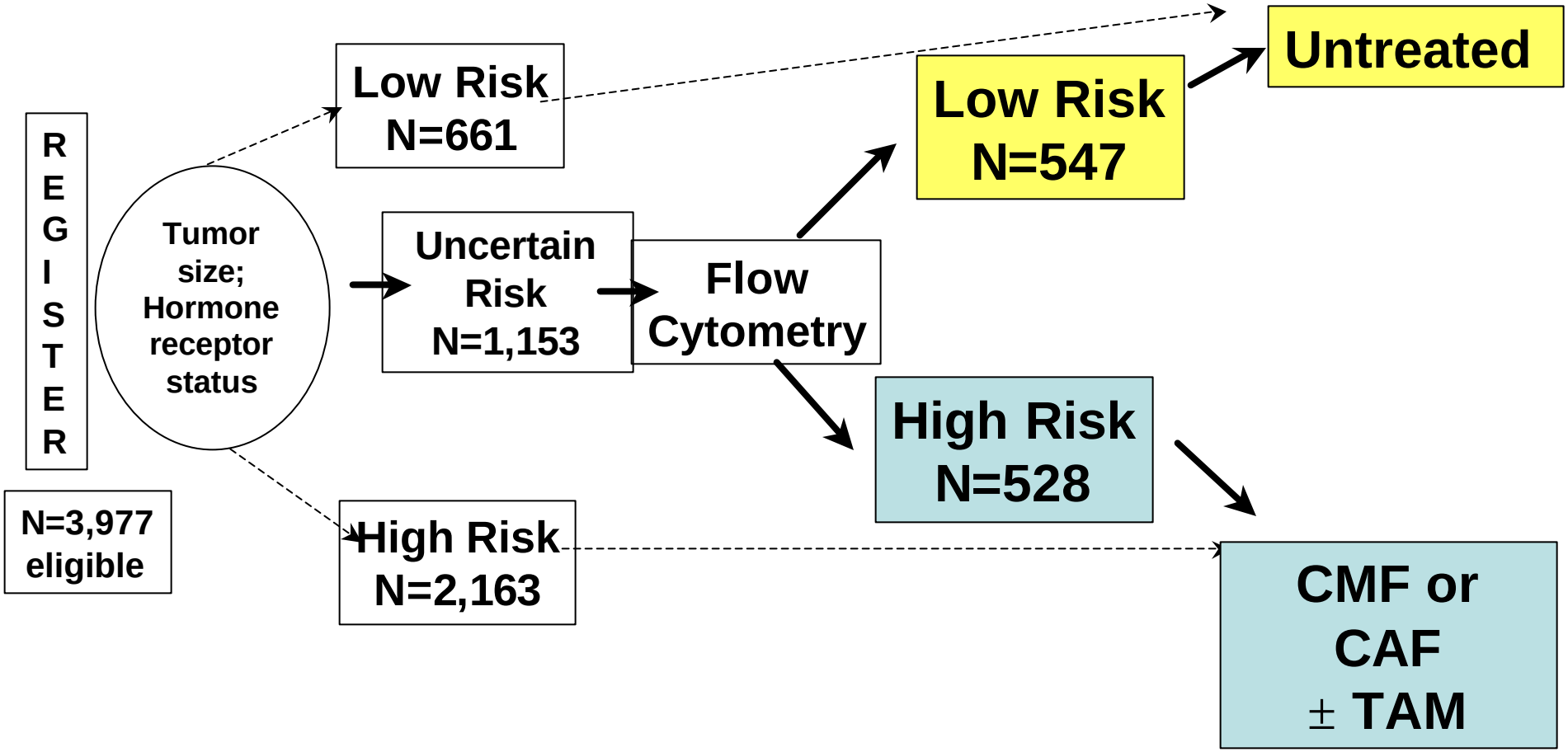
Endogenous Oxidant and Antioxidant Capabilities



- Genes for these enzymes are polymorphic
- SNPs dictate different levels of enzyme activity
- Different genotypes may be sensitive or resistant to chemotherapy

Schema in SWOG S8897

High risk, node negative women (tumor > 2cm *or* negative ER *or* high S phase fraction)

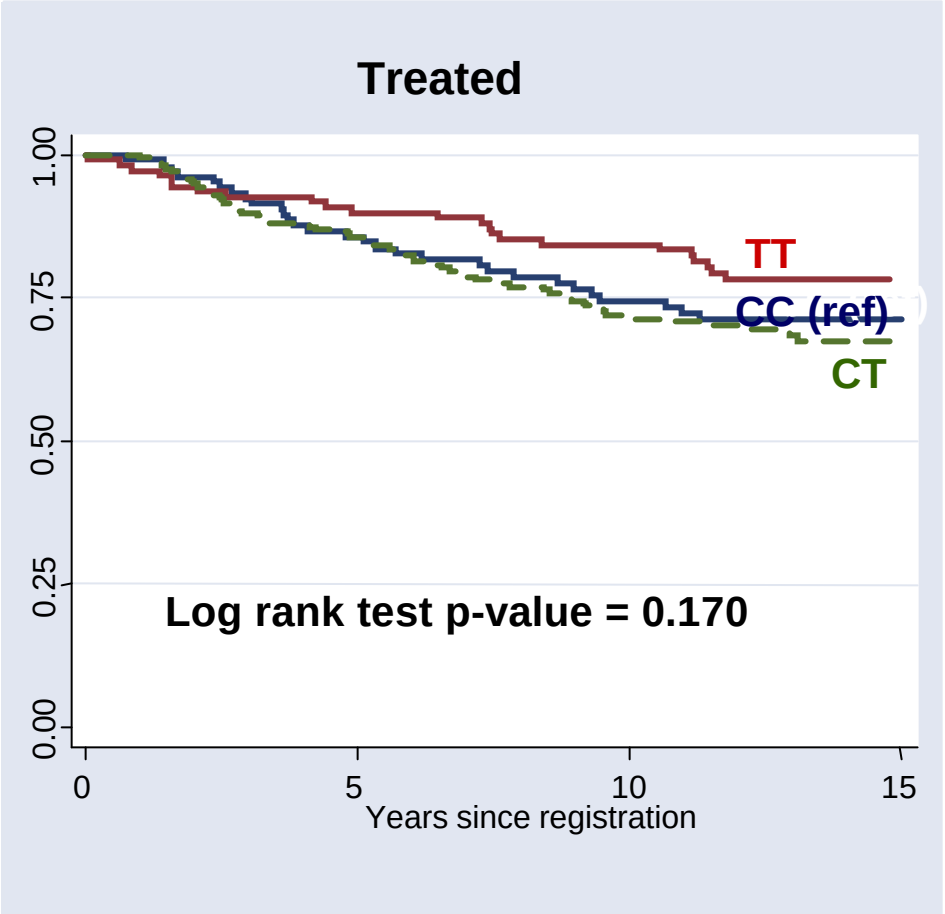


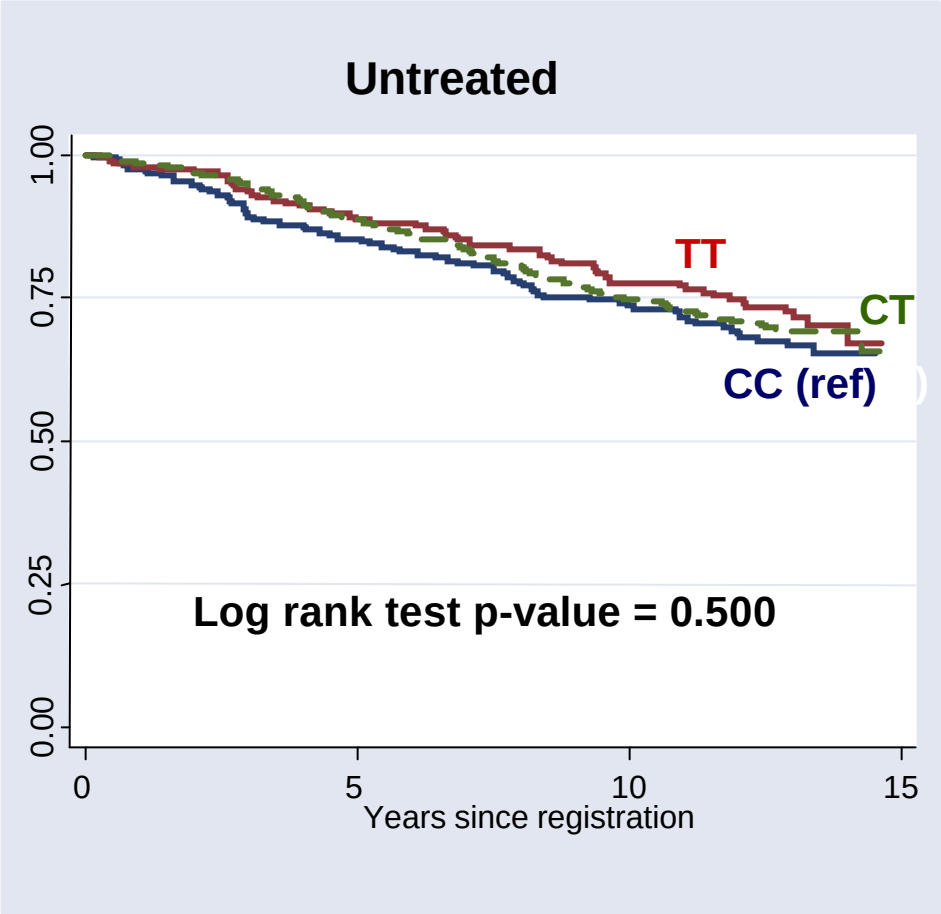
Hutchins et al, JCO 2005; 23:8313-21

Methods

- **Normal lymph node tissue available for genotyping**
  - **Low risk: no treatment**
  - **Intermediate risk: all received chemotherapy (CMF vs. CAF)**
- **Genotyping performed by Ambrosone (RPCI) and Rae laboratories (UMCCC)**

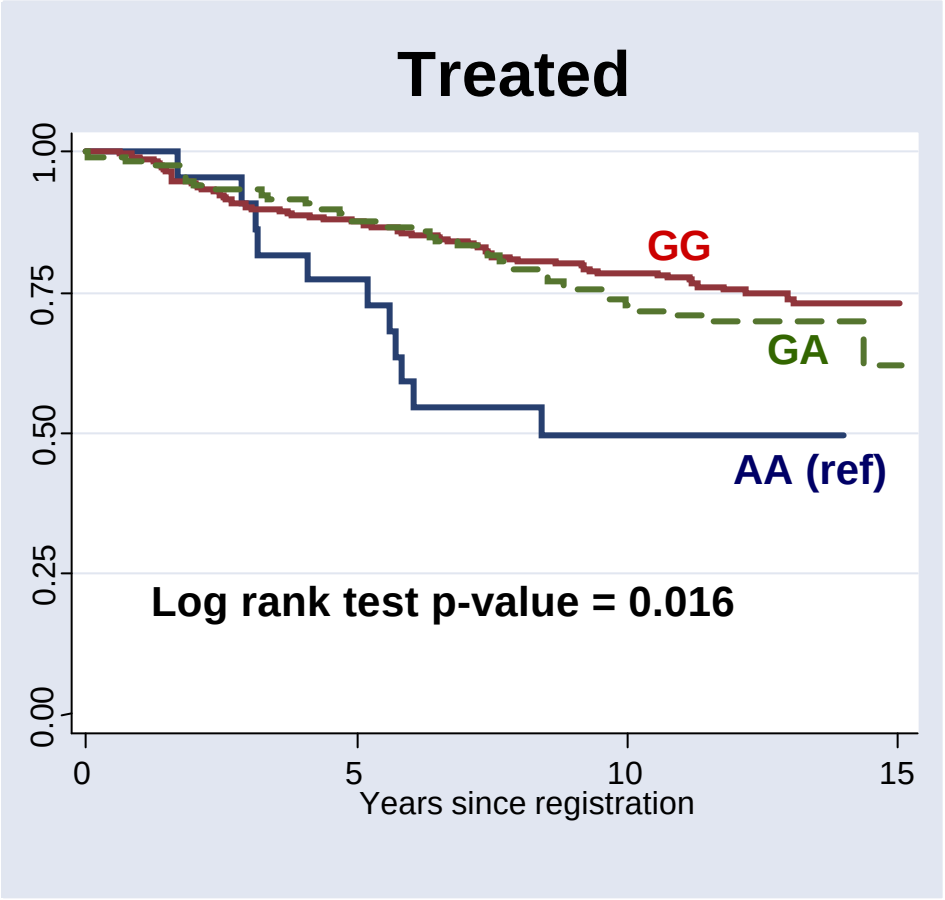
MnSOD C/T (Ala-9Val) and Breast Cancer Disease-Free Survival

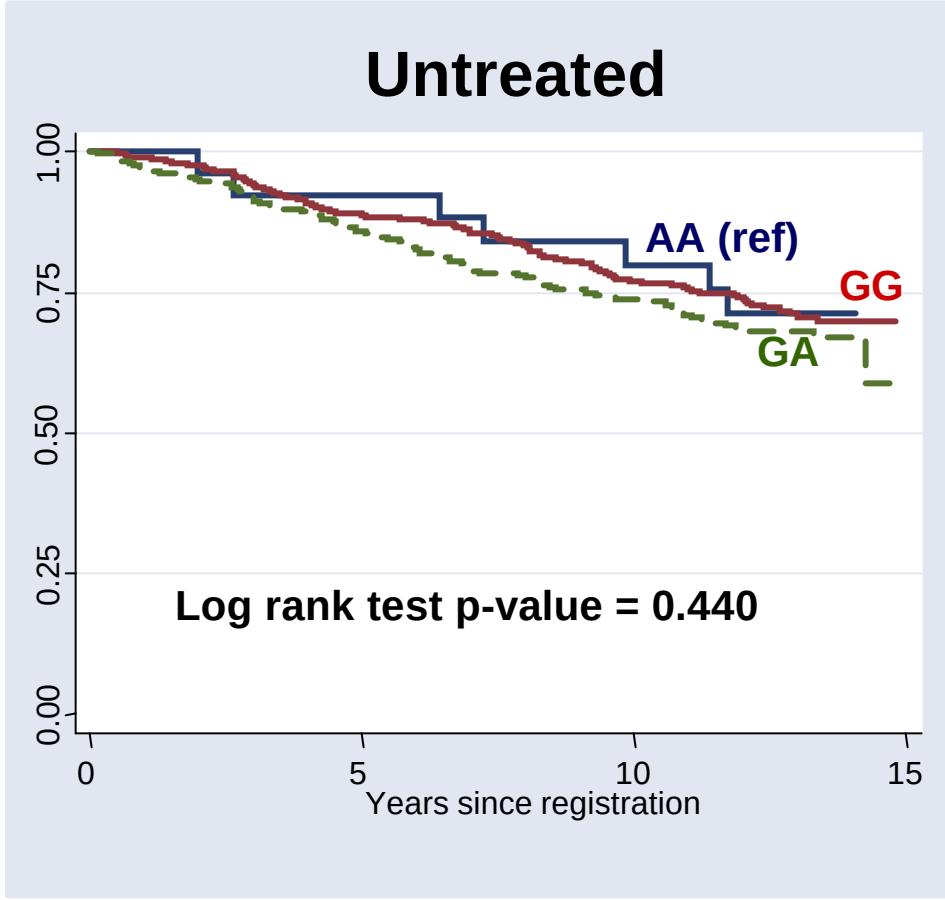




Ambrosone et al San Antonio Breast Cancer Symposium, 2006

MPO -463 G/A and Breast Cancer Disease-Free Survival





Ambrosone et al San Antonio Breast Cancer Symposium, 2006

Associations between *MPO* Genotype and DFS, Treated and Untreated Arms

	Treated			Untreated		
genotype	**censored**	**failures**	**HR (95% CI)**	censored	failures	**HR (95% CI)**
MPO						
AA	**11**	**11**	**1.0 (ref)**	**19**	**7**	**1.0 (ref)**
AG	**84**	**36**	**0.51 (0.26-0.99)**	**169**	**77**	**1.27 (0.59-2.76)**
GG	**194**	**65**	**0.41 (0.21-0.77)**	**350**	**131**	**1.08 (0.50-2.31)**
AA	**11**	**11**	**1.0 (ref)**	**19**	**7**	**1.0 (ref)**
AG+GG	**278**	**101**	**0.44 (0.23-0.82)**	**519**	**208**	**1.14 (0.54-2.43)**

Ambrosone et al San Antonio Breast Cancer Symposium, 2006

HR adjusted for menopausal status, and time between surgery and chemotherapy

Summary and Conclusions

- **High activity *MPO* genotypes are associated with better outcome in women treated with chemotherapy**
  - **Results similar in CMF and CAF groups**
  - **Not PROGNOSTIC (no effect in *untreated* patients)**
- **No effect detected for MnSOD; treated or not**

Limitations

- **Very limited quantities of DNA – only single SNPs assessed**
- **Limited number of genes in pathways examined**
- **Limited sample size**
- **Need for high quality DNA (WBCs) from large clinical trials, comprehensive assessment of variability across genes in pathways**

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S0221: Phase III Trial of Continuous Schedule AC+G vs Q2 Week Schedule AC, Followed by Paclitaxel Given Either Every 2 Weeks or Weekly for 12 Weeks as Post-Operative Adjuvant Therapy in Node-Positive or High-Risk Node Negative Breast Cancer (Budd, PI)

Accrual goal – 3,250

S0221

- **Collection of 2 tubes of blood from consenting patients (1 red-top banked for banked serum, 1 purple top for DNA extraction)**
- **As of 3/27/08, samples received from 903 patients**
- **Also collection of questionnaire data**
- **Application to TBCI for use of DNA for Genome Wide Study in relation to toxicity and DFS**

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SWOG Breast Cancer Pharmacogenomics

- S0702
  - A prospective registry of cancer patients with metastatic bone disease taking bisphosphonate therapy
    - Endpiont: Osteonecrosis of the Jaw (ONJ)
      - PI: Cathy Van Poznak, Julie Gralow
  - n>7000
  - WBC collected and stored on all

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